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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to cytidine 5'-diphosphocholine and maintenance of normal vision pursuant to Article 13(5) of Regulation (EC) No 1924/2006¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2, 3}

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Omikron Italia S.r.l. submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Italy, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to cytidine 5'-diphosphocholine and maintenance of normal vision. The Panel considers that the food constituent cytidine 5'-diphosphocholine (CDP-choline or citicoline), which is the subject of the health claim, is sufficiently characterised. The claimed effect, maintenance of normal vision, is a beneficial physiological effect. The Panel considers that no conclusions can be drawn from the three narrative reviews and the eight human intervention studies provided by the applicant for the scientific substantiation of the claim. The Panel concludes that a cause and effect relationship has not been established between the consumption of CDP-choline and maintenance of normal vision.

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KEY WORDS

cytidine 5'-diphosphocholine, CDP-choline, citicoline, vision, health claims

¹ On request from the Competent Authority of Italy following an application by Omikron Italia S.r.l., Question No EFSA-Q-2013-00757, adopted on 5 February 2014.

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SUMMARY

Following an application from Omikron Italia S.r.l. submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Italy, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to cytidine 5'-diphosphocholine and maintenance of normal vision.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.

The food constituent that is the subject of the health claim is cytidine 5'-diphosphocholine (CDP-choline or citicoline). The Panel considers that the food constituent CDP-choline, which is the subject of the health claim, is sufficiently characterised

The claimed effect proposed by the applicant relates to maintenance (or reduced loss) of normal vision. The target population proposed by the applicant is “elderly subjects since middle age”. The Panel considers that maintenance of normal vision is a beneficial physiological effect.

The applicant identified eight human intervention studies, three reviews, and three non-human studies as being pertinent to the health claim.

The narrative reviews referred to the pharmacological properties of CDP-choline, and to the treatment of glaucoma. Four publications reported on studies in which CDP-choline was administered via intramuscular injection, which is a route of administration that is not relevant to the assessment of health claims made on food. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

The remaining four human intervention studies investigated the effect of oral administration of CDP-choline on several outcome measures in subjects with glaucoma or with non-arteritic ischaemic optic neuropathy.

During the evaluation process, the applicant was requested to clarify how results obtained in subjects with presumed damage to the retinal ganglion cells and/or optic nerve owing to glaucoma or to an ischaemic event could be extrapolated to the target population (i.e. healthy subjects without damaged retinal ganglion cells or optic nerve) for which the claim is made. The Panel notes that no evidence, which could justify the extrapolation of the results obtained in patients with glaucoma or with a non-arteritic ischaemic optic neuropathy to the target population, was provided by the applicant.

The Panel notes that no human intervention studies from which conclusions could be drawn for the scientific substantiation of the claim were provided by the applicant.

The Panel considers that, in the absence of evidence of an effect of CDP-choline on the maintenance of normal vision in humans, the three non-human studies provided cannot be used for the scientific substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of CDP-choline and maintenance of normal vision.

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BACKGROUND

Regulation (EC) No 1924/2006⁴ harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 10/09/2013.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.
- The scientific evaluation procedure started on 04/10/2013.
- On 21/11/2013, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The clock was stopped on 02/12/2013 and was restarted on 17/12/2013, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 18/12/2013, EFSA received the requested information (which was made available to EFSA in electronic format on 16/12/2013).
- During its meeting on 05/02/2014, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to CDP-choline and maintenance of normal vision.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: CDP-choline and maintenance of normal vision.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of CDP-choline, a positive assessment of its safety, nor a decision on whether CDP-choline is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

⁴ Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Omikron Italia S.r.l., Viale Bruno Buozzi, 5, 00197, Rome, Italy.

The application includes a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006. The applicant claimed proprietary rights for the studies by Morreale Bubella et al. (2011) and Ottobelli et al. (2013). The applicant also claimed proprietary rights for information pertaining to the manufacturing process.

Food/constituent as stated by the applicant

According to the applicant, the health claim is made for CDP-choline in oral solution as source of choline as a constituent of a food supplement. Each vial of this food supplement contains 500 mg of CDP-choline in oral solution as source of 102 mg of choline.

Health relationship as claimed by the applicant

According to the applicant, CDP-choline has a positive effect on vision, helping to maintain cellular homeostasis of nervous structures involved in the optic pathways. By protecting the neuronal membranes, CDP-choline showed a secondary effect in helping physiological nervous transmission.

In order to highlight this neuroprotective effect, particularly usable in subjects predisposed to retinal and post-retinal damage, it seems useful to take as a model to perform studies subjects that mimic the normal optical damage detectable with age but in which the damage is accelerated. For this reason, in order to demonstrate the substantiation of the health claim required we will make reference to studies on subjects with glaucoma.

By using electrophysiological methods, it was observed that oral treatment with CDP-choline as a source of choline may induce enhancement of ganglion cell function (objectively evaluated by pattern electroretinogram recordings) and neural conduction along the post-retinal visual pathways (objectively evaluated by visual evoked potential recordings) leading to an improvement of visual function. These results, observed in subjects with glaucoma after two 60-day periods of (oral or intramuscular) treatment with CDP-choline, suggest its potential neuroprotective effect.

The effects of CDP-choline on ophthalmic nervous structures were assessed through several outcome measures: the analysis of efficacy parameters as the slowing of visual field loss or the rebalancing of ophthalmological electrophysiological parameters (visual evoked potential (VEP), pattern electroretinogram (PERG)).

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "CDP-choline in oral solution as source of choline contributes to the maintenance of normal function of the ophthalmic nervous structures".

Specific conditions of use as proposed by the applicant

According to the applicant, the target population is subjects predisposed to retinal and post-retinal damage (> 65 years old, unbalanced diet, subjects with high myopia).

According to the applicant, the suggested daily intake is one vial for a period of four months followed by a two months of wash-out period. This dosage provides 500 mg of CDP-choline in oral solution daily as source of 102 mg of choline, which must be supplemented with a balanced diet.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is proposed by the applicant to be the subject of the health claim is “CDP-choline in oral solution as source of choline as constituent of a food supplement”.

Upon a request from EFSA for clarification, the applicant indicated that the food constituent that is the subject of the health claim is “CDP-choline (monosodium salt) in oral solution”.

Cytidine 5'-diphosphocholine (CDP-choline or citicoline) is a mononucleotide consisting of cytosine, ribose, diphosphate and choline.

CDP-choline can be measured in foods by established methods.

The Panel considers that the food constituent, CDP-choline, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant relates to maintenance (or reduced loss) of normal vision. The target population proposed by the applicant is “subjects predisposed to retinal and post-retinal damage (> 65 years old, unbalanced diet, subjects with high myopia)”.

Upon a request by EFSA for clarification, the applicant indicated that the proposed target population is “elderly subjects since middle age”. The Panel understands the target population to be elderly people in the general population.

From the information provided, the Panel assumed that the mechanism by which CDP-choline could exert the claimed effect (i.e. maintenance (or reduced loss) of normal vision) is “enhancement of the ganglion cell function” and “neural conduction along the post-retinal visual pathways”. However, the Panel noted that, whereas objective measures (i.e. visual evoked potential (VEP) and pattern of electroretinogram (PERG)) had been proposed by the applicant to assess the mechanisms by which CDP-choline could exert the claimed effect, no outcome measures were proposed to evaluate the claimed effect (i.e. visual function) *in vivo* in humans. Upon a request from EFSA for clarification, the applicant indicated that VEP, PERG and the assessment of the visual field are outcome measures related to visual function.

The Panel considers that, whereas visual field assessment is a direct outcome measure of vision, VEP and PERG are used to assess the integrity of cells and nerves involved in visual function but are not measures of vision.

The Panel considers that maintenance of normal vision is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search in PubMed, without specifying the covering period, and using the following key words in various combinations: cytidine diphosphate choline, neuroprotection, visual field, pharmacokinetics, oral. Only publications in English were included.

The applicant identified eight human intervention studies, three narrative reviews, and three non-human studies as being pertinent to the health claim.

The three narrative reviews referred to the pharmacological properties of CDP-choline and to the treatment of glaucoma (Grieb and Rejdak, 2002; Secades, 2011; Chang and Goldberg, 2012). The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

Four publications reported on studies in which CDP-choline was administered via intramuscular injection (Pecori Giraldi et al., 1989; Parisi et al., 1999, 2005; Virno et al., 2000). The Panel notes that parenteral routes of administration are not relevant to the assessment of health claims made on food and considers that these studies do not provide evidence for the scientific substantiation of a claim on dietary CDP-choline.

One double-blind, placebo-controlled study by Morreale Bubella et al. (2011), one open-label randomised controlled study (Parisi et al., 2008) and two uncontrolled (single arm) studies (Rejdak et al., 2003; Ottobelli et al., 2013) investigated the effect of oral administration of CDP-choline on several outcome measures which included VEP, PERG, visual acuity and visual field in subjects with glaucoma (Rejdak et al., 2003; Morreale Bubella et al., 2011; Ottobelli et al., 2013) or with non-arteritic ischaemic optic neuropathy (Parisi et al., 2008).

During the evaluation process, the applicant was requested to clarify how results obtained in subjects with presumed damage to the retinal ganglion cells and/or the optic nerve owing to glaucoma or to an ischaemic event could be extrapolated to the target population (i.e. healthy subjects without damaged retinal ganglion cells and optic nerve) for which the claim is made. In reply the applicant provided two studies: one study described a method for PERG recording in healthy subjects, of different ages, with the purpose of providing normative data for screening and follow-up of glaucoma (Porciatti and Ventura, 2004); the second study investigated how PERG (latency and amplitude) in patients with glaucoma can be reproduced in subjects without glaucoma by amending the conditions of the test (Porciatti and Ventura, 2009). The Panel notes that these studies do not provide evidence which could justify the extrapolation of the results obtained in patients with glaucoma or with a non-arteritic ischaemic optic neuropathy to the target population. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

The Panel notes that no human intervention studies from which conclusions could be drawn for the scientific substantiation of the claim were provided by the applicant.

The applicant also provided one *in vitro* and two animal studies on the effect of CDP-choline on the regeneration of neuritis in mouse retina culture (Oshitari et al., 2002), on concentration of neurotransmitters in retina in rabbits (Rejdak et al. (2002) or on serum CDP-choline concentrations in rats following different routes of administration (Roda et al. 1983). The Panel considers that, in the absence of evidence of an effect of CDP-choline on the maintenance of normal vision in humans, non-human studies cannot be used for the scientific substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of CDP-choline and maintenance of normal vision.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituent CDP-choline, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant relates to maintenance (or reduced loss) of normal vision. The target population proposed by the applicant is “elderly subjects since middle age”. Maintenance of normal vision is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of CDP-choline and maintenance of normal vision.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on CDP-choline and maintenance of normal vision pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0396_IT). September 2013. Submitted by Omikron Italia S.r.l.

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ABBREVIATIONS

CDP-choline Cytidine 5'-diphosphocholine

PERG Pattern of electroretinogram

VEP Visual evoked potential